A Stereoselective Synthesis of Trisubstituted Alkenes. Part 2.[1] The Nickel-catalysed Coupling of Grignard Reagents with 6-Alkyl-3,4-dihydro-2*H*-pyrans and Acyclic Enol Ethers

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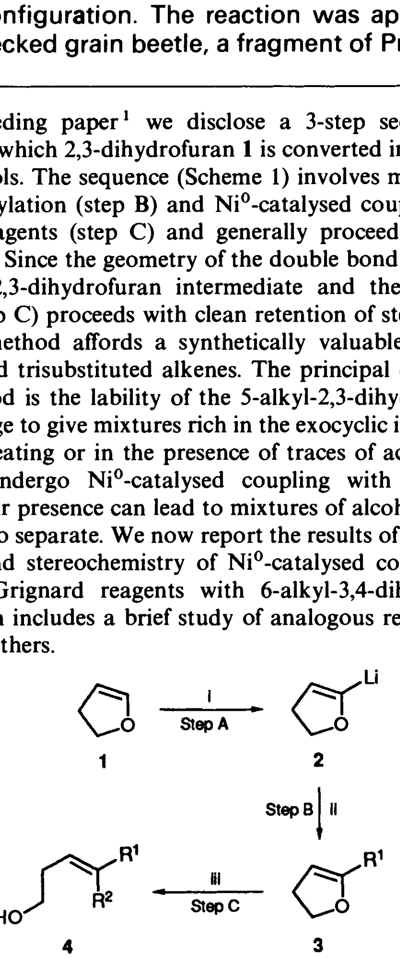
The Ni^0-catalysed coupling of Grignard reagents devoid of β-hydrogens with 6-alkyl-3,4-dihydro-2*H*-pyrans and acyclic enol ethers is highly stereoselective and gives trisubstituted alkenes with retention of configuration. The reaction was applied to syntheses of the aggregation pheromone of the square-necked grain beetle, a fragment of Premonensin B, and the polyketide fragment of Jaspamide.

In the preceding paper[1] we disclose a 3-step sequence of reactions by which 2,3-dihydrofuran **1** is converted into homoallylic alcohols. The sequence (Scheme 1) involves metallation (step A), alkylation (step B) and Ni^0-catalysed coupling with Grignard reagents (step C) and generally proceeds in good overall yield. Since the geometry of the double bond is fixed in the 5-alkyl-2,3-dihydrofuran intermediate and the coupling reaction (step C) proceeds with clean retention of stereochemistry,[2] the method affords a synthetically valuable route to functionalised trisubstituted alkenes. The principal detraction to the method is the lability of the 5-alkyl-2,3-dihydrofurans: they rearrange to give mixtures rich in the exocyclic isomers on prolonged heating or in the presence of traces of acid.[3] Since these too undergo Ni^0-catalysed coupling with Grignard reagents, their presence can lead to mixtures of alcohols which are difficult to separate. We now report the results of a study of the scope and stereochemistry of Ni^0-catalysed coupling reactions of Grignard reagents with 6-alkyl-3,4-dihydro-2*H*-pyrans which includes a brief study of analogous reactions of acyclic enol ethers.



Scheme 1 *Reagents:* i, Bu^tLi–THF; ii, R^1X; iii, R^2MgX, Ni^0

*Preparation of 6-Alkyl-3,4-dihydro-2*H*-pyrans.*—As substrates in the coupling, dihydropyrans have two advantages: they are generally easier to prepare than the corresponding dihydrofurans and they are more stable to heat and mild acid. We have used three methods for preparing 6-alkyl-3,4-dihydro-2*H*-pyrans (Scheme 2). The first (Method A) involves metallation with Bu^tLi followed by alkylation. The metallation reaction with simple dihydropyrans is generally comparable in efficiency and speed to the corresponding reactions with dihydrofurans but the alkylation reactions compare less favourably: they are slower and yields are lower. The formation of 6-pentyl-3,4-dihydro-2*H*-pyran **7a**, for example, proceeded in only 54% overall yield whereas the analogous reaction with 5-lithio-2,3-dihydrofuran **2** exceeded 90%. Alkylation of 6-lithio-2-methoxy-3,4-dihydro-2*H*-pyran **9** was troublesome owing to its instability above −30 °C. Hence acceptable yields required 2 equiv. of dihydropyran **8** and the addition of HMPA (hexamethylphosphoramide) to the reaction mixture. A further complication was the lower yield in the metallation step using 1.1 equiv. of Bu^tLi (*ca.* 70% according to deuteration experiments).

The alkylation step in Method A is restricted to straight chain alkyl iodides or bromides devoid of proximate branching. To a lesser extent the same limitations marred Method B in which 6-alkyl-2,4-dihydropyrans were prepared by a two-step sequence involving addition of a Grignard reagent to a tetrahydropyran-2-one followed by dehydration. The addition was best accomplished in reaction media rich in toluene in order to ensure stability of the ring tautomer of the adduct. As can be seen from Scheme 2, acceptable yields were obtained with straight chain alkyl Grignard reagents but α-branched Grignard reagents such as Bu^iMgBr gave poor yields presumably because of competing reduction.

Method C offered the greatest scope for the appendage of branched chains to dihydropyrans. The method is illustrated by the synthesis of 6-isobutyl-3,4-dihydro-2*H*-pyran **7b** in which a Horner–Wittig reaction of isobutanal with the metallated phosphine oxide **12**[4] gave the exocyclic enol ether **13** as a mixture of isomers which then underwent acid-catalysed rearrangement of the alkene to the more stable endocyclic position.[5] Further examples of the application of all three methods are given below.

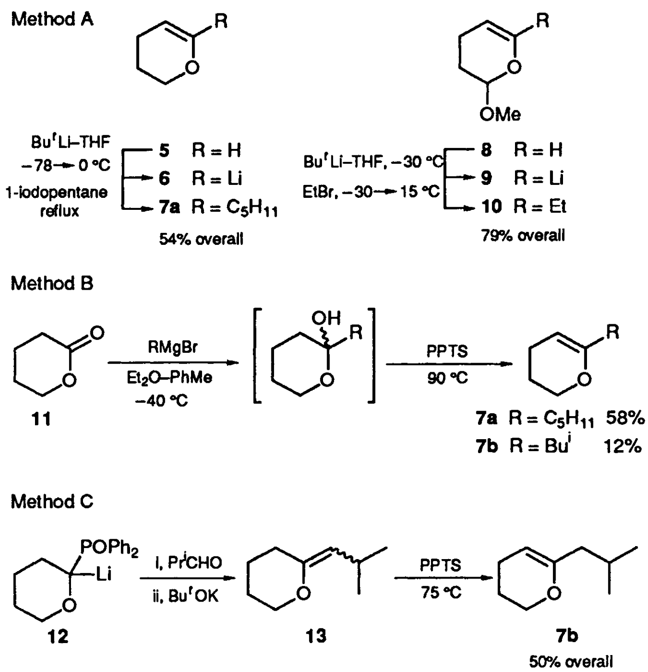
*Ni^0-Catalysed Coupling of Grignard Reagents to 6-Alkyl-3,4-dihydro-2*H*-pyrans.*—An investigation of the scope and stereochemistry of the Ni^0-catalysed coupling of various Grignard reagents with the dihydropyrans **7a** and **7b** [eqn. (1)] using the repertoire of catalyst precursors and reaction conditions previously deployed[1] soon revealed that dihydropyrans are markedly less reactive than the corresponding dihydrofurans. Thus reaction of dihydropyran **7a** with 3 equiv. of MeMgBr in refluxing $PhH–Et_2O$ (*ca.* 5:1) using 3–10 mol% of $(Ph_3P)_2NiCl_2$ as the Ni^0 catalyst precursor returned an 85% yield of alcohol **14a** (Table 1) after 36 h. By contrast the corresponding reaction with 5-pentyl-2,3-dihydrofuran required only 20 min at reflux. Moreover, the low reactivity of Grignard reagents with β-hydrogens (*e.g.*, BuMgBr) previously observed with dihydrofurans altogether precluded reaction with dihydropyrans whose coupling reactions were restricted to Grignard reagents devoid of β-hydrogens such as PhMgBr and Me_3SiCH_2MgCl (see Table 1).

Fortunately, the protracted reaction times did not impair the high stereoselectivity of the coupling (⩾97% retention) though they did exact a toll in overall yield. Capillary gas chromatography revealed that the coupling reaction was initially rapid but slowed markedly after 2 h and virtually stopped after 12 h.

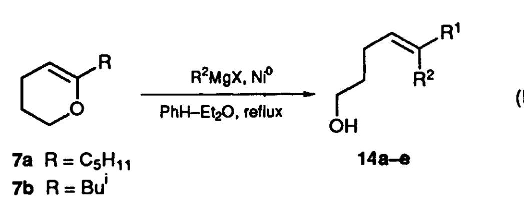
Table 1 Ni^0-Catalysed coupling of Grignard reagents with 3,4-dihydro-2*H*-pyrans **7a, b**

Entry	Dihydropyran	R^1	$R^{2\,a,b}$	Time (h)	Product	Yield (%)[e]
1	**7a**	C_5H_{11}	Me	36	**14a**	85
2	**7a**	C_5H_{11}	Ph	46	**14b**	69
3	**7a**	C_5H_{11}	Me_3SiCH_2	36	**14c**	54
4	**7b**	Bu^i	Me	47[c]	**14d**	35
5	**7b**	Bu^i	Ph	29[d]	**14e**	54

[a] $(Ph_3P)_2NiCl_2$ (10 mol%) was used as the catalyst precursor. [b] 3 Equiv. MeMgBr, PhMgBr and Me_3SiCH_2MgCl were used. [c] Additional aliquots of catalyst (3 mol%) were added after 4, 8 and 24 h. [d] Additional aliquots of catalyst (3 mol%) were added after 7 and 24 h. [e] Yields refer to products purified by column chromatography and Kugelrohr distillation.



Scheme 2

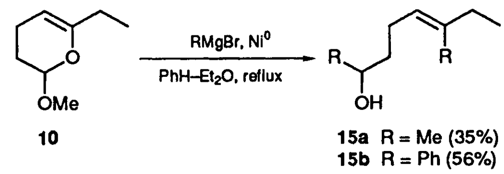


(Eqn. 1)

Thus the reaction never went to completion and the unchanged dihydropyrans gradually decomposed. In such cases (entries 4 and 5, Table 1) it was best to add fresh catalyst in 3 mol% aliquots at various intervals in which case progress of the coupling was restored briefly but never to the same rate as that observed initially.

Reaction of dihydropyran **10** with MeMgBr and PhMgBr (eqn. 2) led to the addition of 2 equiv. of the Grignard reagent. The products **15a, b** could arise by two different mechanisms. In the first the Ni^0-catalysed coupling generates an aldehyde intermediate which subsequently adds a second equivalent of Grignard reagent. Alternatively, $MgBr_2$-assisted displacement of the methoxy group could precede the coupling step.

Ni^0-Catalysed Coupling of Grignard Reagents with Acyclic Enol Ethers.—In order to rule out egregious strain effects in the differential reactivity of dihydrofurans and dihydropyrans, we prepared a series of acyclic enol ethers whose skeleton and substitution approximated the cyclic systems under scrutiny.



(Eqn. 2)

The acyclic enol ethers **18a–d** (Scheme 3) were easily prepared by the method of Takai and co-workers[6] in which the metal carbenoid species **17a–d**, generated by reduction of the 1,1-dibromoalkanes **16a–d**,[7] were condensed with methyl hexanoate. The resultant enol ethers **18a–d** were formed as a mixture of stereoisomers in which the prevalence of the (*Z*)-isomer (80–95%) was ascertained by ^{13}C NMR spectroscopy.*

The coupling reaction of MeMgBr with the acyclic enol ethers **18a–d** was examined under similar conditions used previously for dihydrofurans and dihydropyrans and the course of the reaction was followed by capillary gas chromatography. With $[Ph_3P]_2NiCl_2$ as catalyst precursor, the reactions finished in 16–19 h (Table 2, entries 3, 8 and 11). Thus the acyclic enol ethers were roughly midway in reactivity between dihydropyrans and dihydrofurans giving moderate yields of trisubstituted alkenes **19a–d** with retention of configuration. One important difference between dihydropyrans and acyclic enol ethers was the dependence of the rate on the catalyst ligands. The rate at which dihydropyrans **7a, b** coupled with MeMgBr was essentially impervious to ligand variation whereas the acyclic enol ethers displayed considerable variation. For example 1,2-bis(dimethylphosphino)ethane (dmpe) (Table 2, entries 1 and 9) and acetylacetonate (acac) (entries 2, 7 and 10) promoted complete reaction in under 5 h. Interestingly, $Ni(acac)_2$ was useless for coupling reactions involving cyclic enol ethers whereas it was the champion in terms of yield and rate in the acyclic series. Finally, the range of Grignard reagents which participate in coupling with acyclic enol ethers is similar to the dihydropyrans; *i.e.*, PhMgBr coupled with **18a** but BuMgBr did not.

Synthetic Applications of Ni^0-Catalysed Coupling Reactions.—A synthesis of the aggregation pheromone **23** of the square-necked grain beetle *Cathartus quadricollis* (Scheme 4)[9] illustrates the use of Method B for the synthesis of 2,6-diethyl-3,4-dihydro-2*H*-pyran **21** and it shows that substitution at the 2- and 6-positions of the dihydropyran does not impede the coupling reaction.

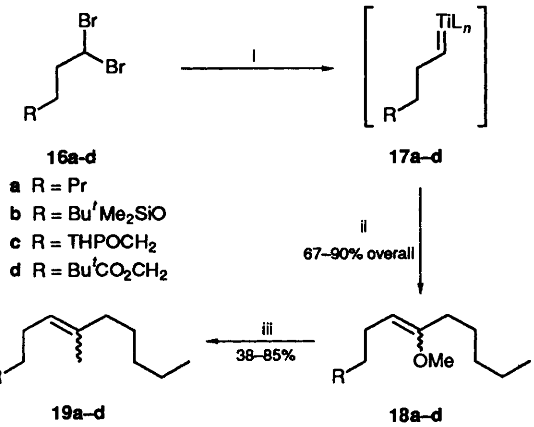
A synthesis of the Premonensin B[10] fragment **29** illustrates the use of two consecutive Ni^0-catalysed coupling reactions for the stereoselective elaboration of polyketide chains and it provides a cogent illustration of the difference in reactivity

* The ^{13}C chemical shift of the β-carbon of (*Z*)-enol ethers (*ca.* δ 106–110) is typically 11–15 ppm downfield of the corresponding (*E*)-isomers.

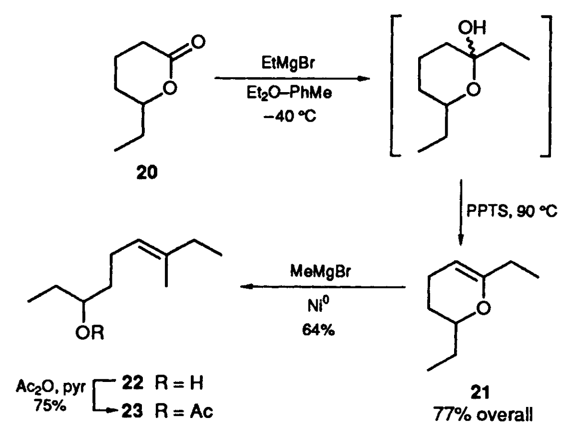
Table 2 Ni^0-Catalysed coupling of MeMgBr with acyclic enol ethers **18a–d**

Entry	Enol ether (*E*:*Z*)[a]	Catalyst precursor[b]	Time (h)	Product (*E*:*Z*)[a]	Yield (%)[c]
1	**18a** (80:20)	(dmpe)$NiCl_2$	5	**19a** (80:20)	69
2	**18a** (80:20)	$Ni(acac)_2$	3	**19a** (92:8)	64
3	**18a** (80:20)	$(Ph_3P)_2NiCl_2$	16	**19a** (83:17)	71
4	**18a** (80:20)	(dppp)$NiCl_2$	23	**19a** (87:13)	60
5	**18a** (80:20)	(dppe)$NiCl_2$	46	**19a** (76:24)	44
6	**18a** (80:20)	(dppf)$NiCl_2$	47	**19a** (85:15)	38
7	**18b** (94:6)	$Ni(acac)_2$	3	**19b** (95:5)	85
8	**18b** (94:6)	$(Ph_3P)_2NiCl_2$	18	**19b** (95:5)	52
9	**18c** (90:10)	(dmpe)$NiCl_2$	3.5	**19c** (92:8)	51
10	**18c** (90:10)	$Ni(acac)_2$	5	**19c** (89:11)	55
11	**18d** (91:9)	$(Ph_3P)_2NiCl_2$	19	**14a** (93:7)	76

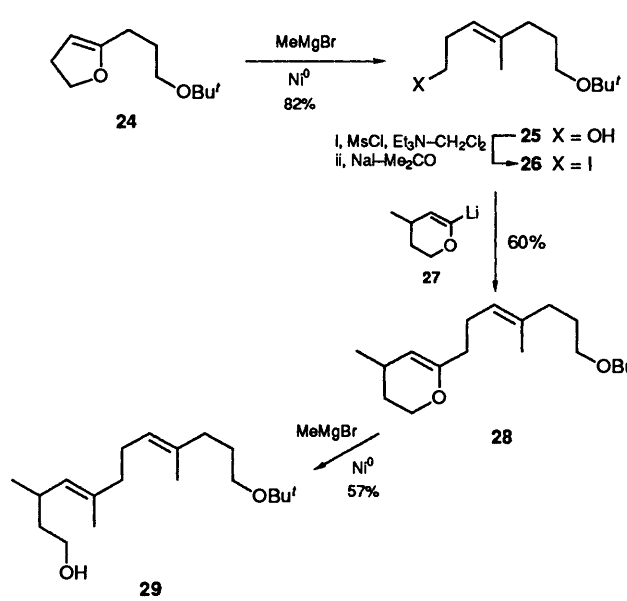
[a] Ratios determined by capillary gas chromatography. [b] dmpe = 1,2-bis(dimethylphosphino)ethane; acac = acetylacetonate; dppp = 1,2-bis-(diphenylphosphino)propane; dppe = 1,2-bis(diphenylphosphino)ethane; dppf = 1,1′-bis(diphenylphosphino)ferrocene. [c] Yield refers to products purified by column chromatography and Kugelrohr distillation.



Scheme 3 *Reagents and conditions:* i, $TiCl_4$, Zn, TMEDA, THF, 20 °C, 2 h; ii, methyl hexanoate; iii, MeMgBr, Ni^0, $PhH–Et_2O$ (5:1), reflux



Scheme 4

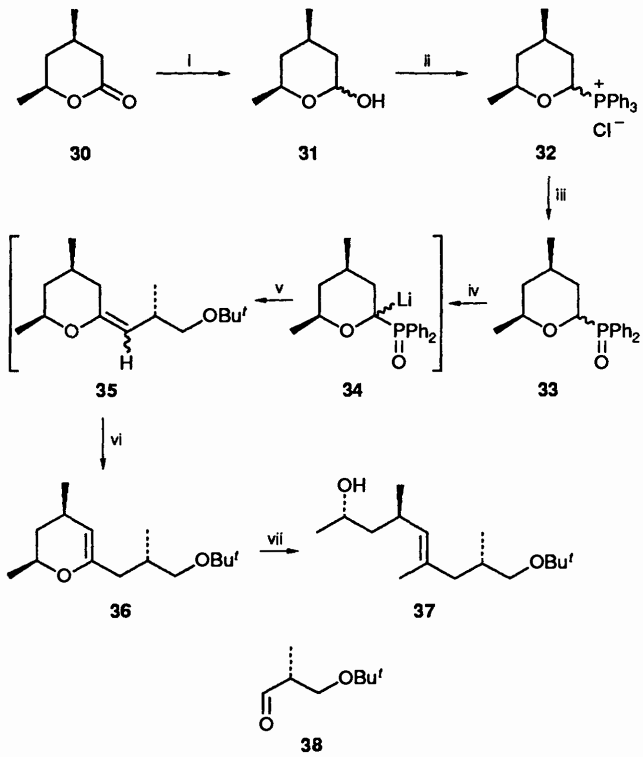


Scheme 5

between dihydropyrans and dihydrofurans. The coupling of dihydrofuran **24** with MeMgBr using $(Ph_3P)_2NiCl_2$ as the catalyst precursor proceeded in 82% yield after only 40 min at reflux in $PhH–Et_2O$ (*ca.* 5:1).[1] The resultant homoallylic alcohol **25** was converted into the corresponding iodoalkene **26** *via* the methanesulfonate ester and then used to alkylate 6-lithio-4-methyl-3,4-dihydro-2*H*-pyran **27**. The comparatively low yield (60%) of **28** from the alkylation step is a consequence of competing elimination of the homoallylic iodoalkene and reflects the lower nucleophilicity of metallated dihydropyrans compared with the analogous dihydrofurans which are known to react with homoallylic iodoalkanes in high yield.[11] The second coupling reaction leading to **29** only gave a 57% yield and required 20 h at reflux as well as supplementation of the catalyst at intervals and even then unchanged dihydrofuran remained when the reaction was terminated. The product **29** was, nevertheless, obtained in acceptable overall yield in good state of stereochemical purity (≥95%, *E,E*).

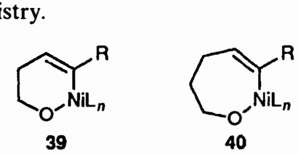
Our synthesis of the polyketide fragment **37**[12] of the marine antifungal agent Jaspamide[13] required a trisubstituted alkene synthesis which would accommodate the branching methyl groups (Scheme 6). Hence, the requisite dihydropyran intermediate **36** was constructed using Method C. (4*R*,6*S*)-4,6-Dimethyltetrahydropyran-2-one **30**[14] was converted into the hygroscopic phosphine oxide **33** in 3 steps (61%) according to established procedures[3] and then united with the known aldehyde **38**[15] *via* a Horner–Wittig reaction. Acid-catalysed rearrangement of the exocyclic double bond into the endocyclic position then afforded the dihydropyran **36**. Unfortunately, all attempts to effect Ni^0-catalysed coupling with MeMgBr under our standard conditions failed to return any of the target **37** but eventually we found that a mediocre yield (31%) could be achieved by conducting the coupling reaction in refluxing toluene for 36 h. Further improvements proved elusive.

The foregoing experiments show that dihydrofurans are conspicuous in their favourable reactivity with a range of Grignard reagents whereas dihydropyrans and acyclic enol ethers only react with Grignard reagents devoid of β-hydrogens. Thus, the relative stability and ease of preparation of 6-alkyl-3,4-dihydro-2*H*-pyrans do not compensate for the narrower scope and diminished reactivity in Ni^0-catalysed coupling



Scheme 6 *Reagents, conditions and yields:* i, Bu^i_2AlH–CH_2Cl_2, −78 °C, 85%; ii, Ph_3P, HCl(g)–PhH, 80%; iii, 3 mol dm^{-3} NaOH, heat, 90%; iv, Pr^i_2NLi–THF, −78 °C; v, (*a*) aldehyde **38**, (*b*) Bu^tOK–THF, room temp.; vi, distil (120 °C)/0.8 mmHg, 60%; vii, MeMgBr, Ni^0PhH–Et_2O (5:1), heat, 36 h, 31%

reactions; hence, dihydrofurans, despite their lability, are the recommended substrates for the elaboration of trisubstituted alkenes. What is the origin of the marked difference in reactivity between dihydrofurans and dihydropyrans in Ni^0-catalysed coupling reactions? Are dihydrofurans atypical in their high reactivity or are dihydropyrans atypically low in reactivity? If we assume that the rate limiting step in the coupling reaction is insertion of Ni^0 into the C–O bond of the enol ether, the higher reactivity of dihydrofurans may be simply the result of slightly higher strain in the 5-membered ring. On the other hand, if we assume that coordination of the π-system of the enol ether precedes Ni^0 insertion, the slightly better p–π interaction in dihydrofurans may be significant.[5] Factors opposing the reactivity of the dihydropyrans may be the steric compression which is a consequence of metal insertion. In the case of dihydrofurans the six-membered ring **39** easily accommodates the square planar Ni and its attendant ligands whereas models show that the seven-membered ring **40** resulting from insertion into the dihydropyran C–O bond is quite strained. In the case of dihydropyran **36**, the methyl group at C-4 introduces transannular strain which is reflected in much diminished reactivity. Whatever the explanation, the reaction of Grignard reagents with enol ethers is remarkable since the C–O bond is widely regarded as one of the most durable functional groups in organic chemistry.



Experimental

For a general description of experimental details see preceding paper.[1]

6-Pentyl-3,4-dihydro-2H-pyran **7a** (*Method A*).—*tert*-Butyllithium (1.7 mol dm^{-3}; 7.0 cm^3, 12 mmol) in pentane was slowly added to a stirred solution of 3,4-dihydro-2*H*-pyran (1.10 g, 13 mmol) in dry THF (3.5 cm^3) at −50 °C under argon. The solution was allowed to warm to 0 °C, stirred for 1 h, cooled to −30 °C and 1-iodopentane (1.98 g, 10 mmol) in dry THF (2 cm^3) was added. The solution was allowed to warm to room temperature, heated to reflux for 1 h, allowed to cool, poured into saturated ammonium chloride–10% ammonia solution (hereafter NH_4Cl–NH_4OH) (25 cm^3) and extracted with Et_2O. The extracts were combined, dried ($MgSO_4$) and evaporated to an oil which was distilled *via* Kugelrohr to give the *title compound* (0.83 g, 5.38 mmol, 54%) as a colourless oil; b.p. 80 °C/15 mmHg; ν_{max}(film)/cm^{-1} 2980s, 2880s, 1680s, 1470s, 1390s, 1350s, 1300m, 1240m, 1160m, 1120s, 1070s, 820s and 740s; δ_H(360 MHz) 4.44 (1 H, t, *J* 3.7), 3.97 (2 H, t, *J* 5), 1.98 (4 H, m), 1.78 (2 H, m), 1.44 (2 H, m), 1.29 (4 H, m) and 0.89 (3 H, t, *J* 7); δ_C(90.6 MHz) 154.92 (s), 94.91 (d), 66.14 (t), 34.47 (t), 31.58 (t), 26.86 (t), 22.76 (t), 22.60 (t), 20.44 (t) and 14.03 (q); *m*/*z* (EI mode) 154 ($M^{+\bullet}$, 9%), 111 (30), 98 (100), 83 (23), 69 (27), 55 (76) and 43 (65).

6-Ethyl-2-methoxy-3,4-dihydro-2H-pyran **10**.—*tert*-Butyllithium (1.7 mol dm^{-3} in pentane) (23.5 cm^3, 20 mmol) was added dropwise to a stirred solution of 2-methoxy-3,4-dihydro-2*H*-pyran (4.57 g, 40 mmol) in dry THF (6.6 cm^3, 80 mmol) under dry argon at −30 °C and the solution stirred for 30 min at this temperature. To the resulting clear dark orange solution dry THF (10 cm^3) and HMPA (7.0 cm^3, 40 mmol) were added dropwise and the thick, dark orange solution stirred for a further 30 min, before bromoethane (2.18 g, 20 mmol) in dry THF (5 cm^3) was added dropwise. The solution was allowed to warm to 15 °C and the decolourised solution was poured into stirred (NH_4Cl–NH_4OH) solution (150 cm^3), extracted with light petroleum, washed (brine), dried ($MgSO_4$), filtered through deactivated basic alumina (6% water) and solvents removed under reduced pressure. The residue was distilled *via* Kugelrohr to give the *title compound* (2.25 g, 15.8 mmol, 79%) as a colourless oil; b.p. 120 °C (oven temp.)/15 mmHg; ν_{max}(film)/ cm^{-1} 2980s, 2950s, 2860s, 1690s, 1665w, 1455m, 1380m, 1245s, 1220s, 1180s, 1130s, 1100s, 1050s, 965m, 920s, 870m and 780m; δ_H(60 MHz; CCl_4) 4.80 (1 H, t, *J* 2.5), 4.45 (1 H, m), 3.45 (3 H, s), 2.3–1.7 (6 H, m) and 1.05 (3 H, t, *J* 7.5) (Found: $M^{+\bullet}$, 156.1155. $C_9H_{16}O_2$ requires *M*, 156.1150).

6-Pentyl-3,4-dihydro-2H-pyran **7a** (*Method B*).—Pentylmagnesium bromide (2 mol dm^{-3} in Et_2O; 75 cm^3, 150 mmol) was added dropwise to a stirred solution of tetrahydropyran-2-one (15.0 g, 150 mmol) in dry toluene (200 cm^3) at −40 °C under nitrogen. The solution was poured into (NH_4Cl–NH_4OH) (500 cm^3), stirred for 1 h and extracted with Et_2O. The Et_2O extracts were combined, dried ($MgSO_4$) and solvents removed under reduced pressure to give a white paste. The paste was heated in a Kugelrohr with PPTS (20 mg) at 25 mmHg and the product distilling at 90–100 °C collected. The distillate was dried ($MgSO_4$) and redistilled *via* Kugelrohr yielding the *title compound* (13.3 g, 86.3 mmol, 58%) as a colourless oil whose spectral data was identical to that produced *via* lithiation and alkylation.

6-Isobutyl-3,4-dihydro-2H-pyran **7b** (*Method C*).—Butyllithium (2.5 mol dm^{-3} in hexane) (8.8 cm^3, 22 mmol) was added dropwise to a stirred solution of diisopropylamine (2.23 g, 22 mmol) in dry THF (5 cm^3) at −60 °C under argon. The mixture was allowed to warm to 0 °C, stirred for 30 min, and re-cooled to −60 °C. A solution of (tetrahydropyran-2-yl)diphenylphosphine oxide[4] (5.73 g, 20 mmol) in dry THF (40 cm^3) was added dropwise and the resulting dark red solution stirred for

1 h at −60 °C. Isobutyraldehyde (1.59 g, 22 mmol) was added dropwise and the solution allowed to warm to room temperature to give a white precipitate in a colourless solution. The mixture was poured into stirred saturated NH_4Cl solution, extracted with $CHCl_3$, dried ($MgSO_4$) and solvents removed under reduced pressure. The residue was dissolved in dry THF (15 cm^3) and a solution of potassium *tert*-butoxide (2.24 g) in dry THF (15 cm^3) was added and the solution stirred for 40 min before removing the solvents under reduced pressure. The residue was dissolved in CH_2Cl_2 and after addition of Et_2O, the solution was filtered through a Celite pad and solvents removed under reduced pressure to leave a red–brown oil which was distilled *via* Kugelrohr at 120–130 °C (oven temp.)/15 mmHg to yield a colourless oil having three isomeric enol ether components in the ratio 53:39:8 [*exo*(*E*):*exo*(*Z*):*endo*] according to capillary GC and 270 MHz ^1H NMR spectroscopy. Isomerisation was accomplished by distilling the mixture **13** on a Kugelrohr apparatus from a catalytic amount of PPTS to give the *title compound* (1.41 g, 10.1 mmol, 50%) as a colourless oil; b.p. 75 °C/15 mmHg; ν_{max}(film)/cm^{-1} 2980s, 1690s, 1480s, 1395s, 1380s, 1360s, 1310s, 1240s, 1180s, 1120s, 1095s, 1080s, 990m, 940s, 900m, 875m, 825s and 775s; δ_H(360 MHz) 4.44 (1 H, t, *J* 3.7), 3.95 (2 H, t, *J* 5.2), 1.99 (2 H, q, *J* 5.6), 1.83 (2 H, d, m), 1.77 (3 H, m) and 0.88 (6 H, dd, *J* 4.3, 2.3); δ_C(90.6 MHz) 153.95 (s), 99.32 (d), 66.14 (t), 44.08 (t), 26.20 (t), 22.78 (t), 22.43 (q) and 20.53 (t) (Found: M^+, 140.1197. $C_9H_{16}O$ requires *M*, 140.1201).

General Procedure for the Ni^0*-Catalysed Coupling of Grignard Reagents with Dihydropyrans.*—(*Z*)-5-*Phenyldec*-4-*en*-1-*ol* **14b**.—MeMgBr (3 mol dm^{-3} in Et_2O; 0.13 cm^3, 0.4 mmol) was added dropwise to a stirred dark green suspension of $(Ph_3P)_2NiCl_2$ (131 mg, 0.2 mmol) in benzene (5 cm^3) under nitrogen at room temperature to effect reduction of the nickel catalyst. The dark red solution was stirred for 15 min whereupon PhMgBr (2 mol dm^{-3} in Et_2O; 3 cm^3, 6 mmol) was added. The solvent was removed under reduced pressure (25 mmHg) and benzene (3 cm^3) was added followed by 6-pentyl-3,4-dihydro-2*H*-pyran **7a** (309 mg, 2 mmol) in benzene (3 cm^3). After refluxing for 46 h, the black mixture was poured into saturated aqueous NH_4Cl, extracted with Et_2O, dried ($MgSO_4$) and solvents removed under reduced pressure. Column chromatography on silica gel and distillation *via* Kugelrohr gave the *title compound* (320 mg, 1.38 mmol, 69%) as a colourless oil; b.p. 170 °C (oven temp.)/0.2 mmHg; ν_{max}(film)/cm^{-1} 3450br s, 3100m, 3080m, 3060m, 2980s, 2880s, 1610m, 1590w, 1500s, 1480s, 1450s, 1390s, 1200m, 1060s, 1040s, 920s, 750s, 710s and 660s; δ_H(360 MHz) 7.29 (2 H, t, *J* 7.4), 7.19 (1 H, t, *J* 7.4), 7.12 (2 H, d, *J* 6.8), 5.42 (1 H, t, *J* 7.4), 3.46 (2 H, t, *J* 6.7), 2.38 (1 H, s, OH), 2.30 (2 H, t, *J* 6.8), 1.96 (2 H, q, *J* 7.4), 1.53 (2 H, tt, *J* 6.8), 1.24 (6 H, m) and 0.84 (3 H, t, *J* 6.8); δ_C (90.6 MHz) 142.10 (s), 141.54 (s), 128.39 (d), 128.17 (d), 126.43 (d), 126.26 (d), 62.32 (t), 39.36(t), 33.09 (t), 31.47 (t), 29.39 (t), 27.85 (t), 25.21 (t) and 14.00 (q); *m*/*z* (EI mode) 232 ($M^{+\bullet}$, 13%), 176 (17), 161 (21), 143 (67), 128 (50), 117 (100), 91 (58) and 77 (7).

By the same general procedure the following coupling reactions were performed using dihydropyran **7a**, **b** (2 mmol), Grignard reagent (6 mmol), and $(Ph_3P)_2NiCl_2$ (0.2 mmol) for the time indicated in Table 1.

(*E*)-5-*Methyldec*-4-*en*-1-*ol* **14a**.—Prepared in 85% yield by the reaction of dihydropyran **7a** with MeMgBr; b.p. 140 °C (oven temp.)/0.1 mmHg; ν_{max}(film)/cm^{-1} 3350br s, 2960s, 2880s, 1470s, 1390s and 1070s; δ_H(360 MHz) 5.12 (1 H, tq, *J* 7.2, 1.3), 3.60 (2 H, t, *J* 6.7), 2.95 (1 H, s, OH), 2.06 (2 H, q, *J* 7.4), 1.96 (2 H, t, *J* 7.6), 1.60 (2 H, m), 1.59 (3 H, br s), 1.4–1.2 (6 H, m) and 0.88 (3 H, t, *J* 7.1); δ_C(90.6 MHz) 136.15 (s), 123.64 (d), 62.50 (t), 39.71 (t), 32.90 (t), 31.58 (t), 27.72 (t), 24.32 (t), 22.56 (t), 15.83 (q) and 13.97 (q); *m*/*z* (EI mode) 170 ($M^{+\bullet}$, 11%).

(*Z*)-5-*Trimethylsilylmethyldec*-4-*en*-1-*ol* **14c**.—Prepared in 54% yield by the reaction of dihydropyran **7a** with Me_3SiCH_2MgCl; b.p. 200 °C (oven temp.)/15 mmHg; ν_{max}(film)/cm^{-1} 3320br, 2960, 2940, 2860, 1470, 1420, 1380, 1250, 1160, 1060, 860 and 700; δ_H(360 MHz) 4.97 (1 H, t, *J* 6.1), 3.64 (2 H, t, *J* 6.1), 2.00 (2 H, q, *J* 6.2), 1.90 (2 H, t, *J* 6.2), 1.85 (1 H, br s), 1.60 (2 H, tt, *J* 6.1), 1.52 (2 H, s), 1.2–1.4 (6 H, m), 0.88 (3 H, t, *J* 6.3) and 0.0 (9 H, s); δ_C(90.6 MHz) 138.17 (s), 120.84 (d), 62.92 (t), 39.27 (t), 33.20 (t), 31.81 (t), 28.09 (t), 24.91 (t), 22.68 (t), 21.46 (t), 14.10 (q) and −0.53 (q); *m*/*z* (EI mode) 242 ($M^{+\bullet}$, 44%).

(*E*)-5,7-*Dimethyloct*-4-*en*-1-*ol* **14d**. Prepared in 35% yield by the reaction of dihydropyran **7b** with MeMgBr; b.p. 105 °C (oven temp.)/6 mmHg; ν_{max}(film)/cm^{-1} 3320br s, 2960s, 1470m, 1390m, 1370m and 1065m; δ_H(270 MHz) 5.11 (1 H, t, *J* 7.2), 3.65 (2 H, t, *J* 6.5), 2.09 (2 H, q, *J* 7.2), 1.84 (2 H, d, *J* 7.1), 1.75 (1 H, m), 1.62 (2 H, tt, *J* 6.8), 1.57 (3 H, s), 1.50 (1 H, s, OH) and 0.83 (6 H, d, *J* 6.4); δ_C(67.5 MHz) 135.19 (s), 125.05 (d), 62.85 (t), 49.70 (t), 32.92 (t), 26.07 (d), 24.33 (q), 22.51 (q) and 15.95 (q); *m*/*z* (EI mode) 156 ($M^{+\bullet}$, 1.7%), 109 (2.1), 95 (17.1), 83 (14.4), 67 (15.3), 55 (16.4) and 41 (13.7).

(*Z*)-7-*Methyl*-5-*phenyloct*-4-*en*-1-*ol* **14e**. Prepared in 54% yield by the reaction of dihydropyran **7b** with PhMgBr; b.p. 200 °C (oven temp.)/15 mmHg; ν_{max}(film)/cm^{-1} 3350br s, 2975s, 1610w, 1500m, 1470s, 1450s, 1390m, 1370m, 1065s, 785m and 710s; δ_H(360 MHz) 7.28 (2 H, t, *J* 7.4), 7.18 (1 H, t, *J* 7.4), 7.12 (2 H, d, *J* 6.8), 5.4 (1 H, t, *J* 7.4), 3.47 (2 H, t, *J* 6.7), 2.30 (1 H, s, OH), 2.20 (2 H, d, *J* 7.6), 1.99 (2 H, q, *J* 7.4), 1.54 (2 H, tt, *J* 6.9), 1.45 (1 H, m) and 0.83 (6 H, d, *J* 6.6); δ_C(90.6 MHz) 141.44 (s), 140.93 (s), 128.41 (d), 128.08 (d), 127.69 (d), 126.44 (d), 62.32 (t), 49.20 (t), 33.09 (t), 26.02 (d), 25.12 (t) and 22.33 (q).

(*E*)-6-*Methyloct*-5-*en*-2-*ol* **15a**. Prepared in 35% yield by the reaction of dihydropyran **10** with MeMgBr over 24 h. Owing to gradual catalyst deterioration, additional aliquots of catalyst (3 mol% each) were added after 2, 4, 6, 8 and 23 h. The *title compound* gave b.p. 150–160 °C (oven temp.)/15 mmHg; ν_{max}(film)/cm^{-1} 3460br s, 2980s, 2940s, 1475m, 1380m, 1135m and 1085m; δ_H(360 MHz) 5.13 (1 H, t, *J* 7.2), 3.81 (1 H, tq, *J* 6.2), 2.08 (2 H, td, *J* 7.0), 1.99 (2 H, q, *J* 7.5), 1.76 (1 H, br s, OH), 1.62 (3 H, s), 1.50 (2 H, m), 1.19 (3 H, d, *J* 6.2) and 0.98 (3 H, t, *J* 7.5); δ_C(90.6 MHz) 137.60 (s), 122.66 (d), 68.01 (d), 39.41 (t), 32.43 (t), 24.41 (t), 23.50 (q), 15.89 (q) and 12.79 (q); *m*/*z* (EI mode) 142 ($M^{+\bullet}$, 37%), 124 (42), 109 (48), 95 (100), 83 (55), 67 (61), 55 (78), 45 (46) and 41 (54).

(*Z*)-1,5-*Diphenylhept*-4-*en*-1-*ol* **15b**. Prepared in 56% yield by the reaction of dihydropyran **10** with PhMgBr over 24 h. Owing to gradual catalyst deterioration, additional aliquots of catalyst (3 mol% each) were added after 1, 3, 18, 20 and 23 h. The *title compound* gave b.p. 220 °C (oven temp.)/0.3 mmHg; ν_{max}(film)/cm^{-1} 3500br s, 3040m, 3020m, 2980s, 2890m, 1610w, 1500s, 1470s, 1460s, 1070m, 1035m, 775s and 710s; δ_H(360 MHz) 7.3–7.1 (10 H, m), 5.40 (1 H, tt, *J* 7.3, 1.35), 4.48 (1 H, dd, *J* 5.69, 5.65), 2.32 (2 H, q, *J* 7.44), 2.12 (1 H, br s, OH), 2.05–1.9 (2 H, m), 1.8–1.6 (2 H, m) and 0.94 (3 H, t, *J* 7.4); δ_C(90.6 MHz) 144.75 (s), 141.47 (s), 128.39 (d), 128.12 (d), 127.40 (d), 126.49 (d), 125.94 (d), 125.15 (d), 74.05 (d), 39.48 (t), 32.18 (t), 25.31 (t) and 13.15 (q); *m*/*z* (EI mode) 266 ($M^{+\bullet}$, 69%), 248 (39), 237 (10), 219 (78), 204 (6), 157 (54), 145 (99), 129 (83), 120 (100), 107 (52), 91 (86) and 79 (61).

General Procedure for the Synthesis of Acyclic Enol Ethers via *Reductive Coupling of* 1,1-*Dibromoalkanes with Methyl Hexanoate.*—(*Z*)-5-*Methoxy*-1-*pivaloyloxydec*-4-*ene* **18d**. Freshly distilled $TiCl_4$ (1.76 cm^3, 16 mmol) was added dropwise to stirred dry THF (35 cm^3) under argon at 0–5 °C to form a bright yellow precipitate. After allowing to warm to room temperature, freshly distilled TMEDA (4.8 cm^3, 32 mmol) was added dropwise to form a brown solution with a yellow precipitate. After stirring for 10 min, freshly activated Zn dust (2.35 g, 36 g atom) was added in one portion (exotherm) to form a dark blue solution, which on stirring for 30 min, became dark green. A solution of 1,1-dibromo-4-pivaloyloxybutane **16d** (2.78 g, 8.8 mmol) and methyl hexanoate (520 mg, 4 mmol) in dry THF (5 cm^3) was added and the solution stirred at room temperature for 2–4 h. The solution was then cooled to 0–5 °C and saturated K_2CO_3 solution (3.6 cm^3) added dropwise. After 10 min the thick, black solution was diluted with Et_2O (20 cm^3) and filtered through deactivated basic alumina (6% w/w water) with the aid of Et_2O containing 1% triethylamine. The filtrate was concentrated under reduced pressure and the colourless residue purified by column chromatography on deactivated basic alumina (6% w/w water) using light petroleum as eluent to yield the *title compound* (720 mg, 2.67 mmol, 67%) as a mixture of two isomers (Z:E = 91:9) by capillary GC (190 °C); b.p. 150–155 °C (oven temp.)/0.4 mmHg; ν_{max}(film)/cm^{-1} 2980s, 2960s, 2880m, 1740s, 1690m, 1490m, 1470m, 1300s and 1170s; δ_H(270 MHz) (Z isomer only) 4.47 (1 H, t, J 7), 4.04 (2 H, t, J 6.6), 3.50 (3 H, s), 2.15–2.05 (4 H, m), 1.7–1.6 (2 H, m), 1.45–1.4 (2 H, m), 1.35–1.25 (4 H, m), 1.19 (9 H, s) and 0.88 (3 H, t, J 6.5); δ_C(67.5 MHz) (Z isomer only) 178.8 (s), 155.93 (s), 108.10 (d), 64.13 (t), 56.18 (q), 38.79 (s), 31.47 (t), 31.17 (t), 29.05 (t), 27.27 (t), 26.95 (t), 22.57 (t), 21.13 (t) and 14.11 (q).

By the same general procedure the following enol ethers were prepared by reductive coupling (Scheme 6) of 1,1-dibromoalkanes **16a–c** (8.8 mmol) and methyl hexanoate (4 mmol).

(Z)-6-*Methoxydodec*-6-*ene* **18a**. Prepared in 67% yield as a mixture of isomers (Z:E = 80:20) by the reductive coupling of 1,1-dibromohexane **16a** and methyl hexanoate:[6] ν_{max}(film)/cm^{-1} 2960s, 2940s, 2860s, 1685s, 1470s, 1380m, 1220m, 1120s, 1080s, 790m and 740m; δ_H(90 MHz) 4.5 (1 H, t, J 7), 3.5 (3 H, s), 2.2–1.9 (4 H, m) and 1.5–1.1 (12 H, m) and 0.95–0.85 (6 H, m).

(Z)-1-(tert-*Butyldimethylsiloxy*)-4-*methoxynon*-3-*ene* **18b**. Prepared in 85% yield as a mixture of isomers (Z:E = 94:6) by the reductive coupling of 1,1-dibromo-3-(*tert*-butyldimethylsilyloxy)propane **16b** and methyl hexanoate; ν_{max}(film)/cm^{-1} 2960s, 2870s, 1680m, 1470s, 1260s, 1100s 840s and 780s; δ_H(270 MHz) 4.52 (1 H, t, J 7.2), 3.58 (2 H, t, J 7.05), 3.53 (3 H, s), 2.29 (2 H, dt, J 7.1), 2.10 (2 H, t, J 7.5), 1.30 (6 H, m), 0.85 (12 H, m) and 0.05 (6 H, m); δ_C(67.5 MHz) 156.68 (s), 105.62 (d), 63.58 (t), 56.52 (q), 31.62 (t), 31.44 (t), 28.87 (t), 27.04 (t), 26.19 (q), 22.70 (t), 18.60 (s), 14.22 (q) and −5.03 (q).

(Z)-5-*Methoxy*-1-(*tetrahydropyran*-2-*yloxy*)*dec*-4-*ene* **18c**. Prepared in 84% yield as mixture of isomers (Z:E = 90:10) by the reductive coupling of 1,1-dibromo-4-(tetrahydropyran-2-yloxy)butane **16c** and methyl hexanoate: ν_{max}(film)/cm^{-1} 2950s, 2880s, 1680s, 1470s, 1460s, 1445s, 1360s, 1210s, 1140s, 1125s, 1080s, 1040s, 1000s, 870s and 820s; δ_H(270 MHz) 4.58 (1 H, m), 4.50 (1 H, t, J 7.1), 3.9–3.8 (2 H, m), 3.8–3.7 (1 H, m), 3.51 (3 H, s), 2.15–2.05 (4 H, m), 1.9–1.3 (12 H, m) and 0.90 (3 H, t, J 6.5); δ_C(67.5 MHz) 155.63 (s), 109.19 (d), 98.96 (d), 67.45 (t), 62.37 (t), 56.45 (q), 31.56 (t), 31.41 (t), 30.94 (t), 30.28 (t), 27.05 (t), 25.68 (t), 22.67 (t), 21.61 (t), 19.78 (t) and 14.19 (q).

Ni^0-*Catalysed Coupling of* MeMgBr *with Acyclic Enol Ethers* **18a–d**.—Using the same general procedure described above for the Ni^0-catalysed coupling of MeMgBr with 6-pentyl-3,4-dihydro-2H-pyran **7a**, the following alkenes were prepared as mixtures of isomers using the catalysts and reaction times summarised in Table 2.

(E)-6-*Methyldodec*-6-*ene* **19a**. B.p. 140–150 °C (oven temp.)/15 mmHg; ν_{max}(film)/cm^{-1} 2980s, 2960s, 2860s, 1470s and 1380s; δ_H(270 MHz) 5.13 (1 H, t, J 6.5), 1.97 (4 H, t, J 7), 1.59 (3 H, s), 1.30 (12 H, m) and 0.90 (6 H, t, J 7).

(E)-1-(tert-*Butyldimethylsiloxy*)-4-*methylnon*-3-*ene* **19b**. ν_{max}(film)/cm^{-1} 2960s, 2930s, 2860s, 1470s, 1465s, 1380m, 1340m, 1260s, 1100s, 1010m, 940s, 840s, 780s and 670m; δ_H(270 MHz) 5.12 (1 H, t, J 7.2), 3.59 (2 H, t, J 7.2), 2.23 (2 H, dt, J 7.2), 1.97 (2 H, t, J 6.8), 1.61 (3 H, s), 1.4–1.2 (6 H, m), 0.90 (9 H, s), 0.92–0.88 (3 H, m) and 0.06 (6 H, s); δ_C(67.5 MHz) 137.62 (s), 120.15 (d), 63.36 (t), 39.89 (t), 32.03 (t), 31.73 (t), 27.79 (t), 26.16 (q), 22.77 (t), 18.58 (s), 16.24 (q), 14.27 (q) and −5.04 (q).

(E)-5-*Methyldec*-4-*en*-1-*ol tetrahydropyranyl ether* **19c**. ν_{max}(film)/cm^{-1} 2960s, 2880s, 1470s, 1450s, 1440s, 1390m, 1360s, 1210s, 1150s, 1130s, 1090s, 1040s, 910m, 880m and 820m; δ_H(270 MHz) 5.12 (1 H, t, J 7.2), 4.58 (1 H, t, J 4), 3.92–3.83 (1 H, m), 3.73 (1 H, dt, J 9.7, 6.8), 3.55–3.45 (1 H, m), 3.38 (1 H, dt, J 9.6, 6.7), 2.1–2.0 (2 H, m), 1.96 (2 H, t, J 7.5), 1.7–1.5 (6 H, m), 1.59 (3 H, s), 1.4–1.2 (6 H, m) and 0.88 (3 H, t, J 7.1); δ_C(270 MHz) 136.02 (s), 123.81 (d), 99.00 (d), 67.27 (t), 62.43 (t), 39.84 (t), 31.67 (t), 30.95 (t), 30.07 (t), 27.81 (t), 25.70 (t), 24.66 (t), 22.76 (t), 19.82 (t), 16.02 (q) and 14.27 (q).

Synthesis of the Aggregation Pheromone of the Square-necked Grain Beetle Cathartus quadricollis **23**

2,6-*Diethyl*-3,4-*dihydro*-2H-*pyran* **21**.—The *title compound* (2.57 g, 18.3 mmol, 77%) was prepared by the reaction of EtMgBr (2 mol dm^{-3} in Et_2O, 11.7 cm^3, 23.4 mmol) and 6-ethyltetrahydropyran-2-one **20** (3.0 g, 23.4 mmol) according to method B (*vide supra*); b.p. 110 °C (oven temp.)/15 mmHg; ν_{max}(film)/cm^{-1} 2980s, 2960s, 2860s, 1730w, 1690s, 1475s, 1380m, 1350m, 1315s, 1245s, 1180m, 1125s, 1090s, 1035s, 930s, 780m and 760m; δ_H(270 MHz) 4.44 (1 H, m), 3.73–3.63 (1 H, m), 2.05–1.95 (4 H, m), 1.84–1.74 (1 H, m), 1.63 (1 H, dq, J 14, 7), 1.54 (1 H, dq, J 14, 7), 1.54–1.4 (1 H, m), 1.02 (3 H, t, J 7.4) and 0.97 (3 H, t, J 7.4); δ_C(67.5 MHz) 155.87 (s), 93.40 (d), 76.61 (d), 28.09 (t), 27.30 (t), 27.08 (t), 20.37 (t), 11.67 (q) and 9.82 (q) (Found: M^+, 140.1203. $C_9H_{16}O$ requires M, 140.1201).

(E)-7-*Methylnon*-6-*en*-3-*ol* **22**.—The *title compound* (600 mg, 3.84 mmol, 64%) was prepared by the general procedure described above for the synthesis of **14a**, using 2,6-diethyl-3,4-dihydro-2H-pyran **21** (982 mg, 7 mmol), MeMgBr (6 mmol) and $(Ph_3P)_2NiCl_2$ (3 mol%) as catalyst. Additional aliquots of catalyst (3 mol%) were added after 1, 2, 4 and 17 h (total reaction time = 20 h); b.p. 140–150 °C (oven temp.)/15 mmHg; ν_{max}(film)/cm^{-1} 3360br s, 2975s, 2940s, 2885s, 1460m, 1380m, 1120m, 970m and 850m; δ_H(270 MHz) 5.14 (1 H, t, J 7.2), 3.53 (1 H, tt, J 7.3, 4.8), 2.10 (2 H, td, J 7.4), 1.98 (2 H, q, J 7.4), 1.67 (1 H, br s, OH), 1.62 (3 H, s), 1.52–1.4 (4 H, m), 0.98 (3 H, t, J 7.4) and 0.94 (3 H, t, J 7.4); δ_C(67.5 MHz) 137.62 (s), 122.66 (d), 73.21 (d), 36.90 (t), 32.39 (t), 30.21 (t), 24.32 (t), 15.95 (q), 12.80 (q) and 9.95 (q) (Found: C, 76.5; H, 12.6. $C_{10}H_{20}O$ requires C, 76.85; H, 12.90%).

(E)-3-*Acetoxy*-7-*methylnon*-6-*ene* **23**.—(E)-7-Methylnon-6-en-3-ol **22** (200 mg, 1.3 mmol) was acetylated in the usual way using excess Ac_2O in pyridine in the presence of catalytic amount of DMAP to give the *title compound* (190 mg, 0.95 mmol, 74%) as a colourless oil: b.p. 150–170 °C (oven temp.)/15 mmHg; ν_{max}(film)/cm^{-1} 2980s, 2940s, 2890m, 1750s, 1465m, 1380m, 1250s, 1030m and 960m; δ_H(270 MHz) 5.08 (1 H, t, J 7.2), 4.81 (1 H, tt, J 6.5, 5.8), 2.04 (3 H, s), 1.98 (4 H, m), 1.6–1.5 (4 H, m), 1.57 (3 H, s), 0.97 (3 H, t, J 7.5) and 0.88 (3 H, t, J 7.5); δ_C(67.5 MHz) 171.98 (s), 137.37 (s), 122.08 (d), 75.26 (d), 33.69 (t), 32.36 (t), 27.01 (t), 23.84 (t), 21.29 (q), 15.88 (q), 12.78 (q) and 9.59 (q) (Found: C, 72.55; H, 11.0. $C_{12}H_{22}O_2$ requires C, 72.68; H, 11.19%).

Synthesis of a Fragment of Promensin B **29**

(E)-7-tert-*Butoxy*-1-*iodo*-4-*methylhept*-3-*ene* **26**.—Methanesulfonyl chloride (1.35 cm^3, 17.5 mmol) was added dropwise to a solution of (*E*)-7-*tert*-butoxy-4-methylhept-3-en-1-ol **25** (2.70 g, 13.5 mmol) and Et_3N (5.6 cm^3, 40 mmol) in dry CH_2Cl_2 (25 cm^3) stirred at 0 °C under dry nitrogen. After addition was complete, the mixture was stirred for 30 min. 1,1-Dimethylaminopropylamine (2.0 cm^3, 16 mmol) was then added dropwise and the mixture stirred at room temperature for 5 min before being poured into water. The mixture was extracted with Et_2O and the combined extracts concentrated to a yellow oil containing the crude methanesulfonate which was taken up in acetone (200 cm^3). Sodium iodide (12.2 g, 81 mmol) was added and the mixture heated to reflux to give a yellow solution. After 4 h, removal of the solvent gave a residue which was partitioned between water and Et_2O. The aqueous phase was extracted with Et_2O and the combined organic extracts were dried ($MgSO_4$) and evaporated to leave a yellow oil. Filtration through a plug of silica, eluting with light petroleum, followed by evaporation gave the *title compound* **26** (3.85 g, 97%) as a colourless oil which decomposed on standing: ν_{max}(film)/cm^{-1} 2970s, 2930s, 2860s, 1725w, 1660w, 1360s, 1240s, 1200s and 1080s; δ_H(270 MHz) 5.09 (1 H, tq, *J* 1.2, 7.1), 3.30 (2 H, t, *J* 6.8), 3.09 (2 H, t, *J* 7.2), 2.56 (2 H, dt, *J* 7.1, 7.2), 2.01 (2 H, t, *J* 7.5), 1.67–1.58 (2 H, m), 1.59 (3 H, s) and 1.16 (9 H, s); δ_C(67.5 MHz) 137.8 (s), 122.9 (d), 72.5 (s), 61.0 (t), 36.1 (t), 32.3 (t), 28.5 (t), 27.6 (q), 16.3 (q) and 6.2 (t). The iodoalkane was best used immediately in the next step.

6-[(E)-7-tert-*Butoxy*-4-*methylhept*-3-*enyl*]-4-*methyl*-3,4-*dihydro*-2H-*pyran* **28**.—A solution of *tert*-butyllithium in pentanes (2.6 cm^3, 4.4 mmol) was added dropwise to a solution of 4-methyl-3,4-dihydro-2*H*-pyran[16] (0.36 g, 3.7 mmol) in dry THF (0.71 cm^3, 8.8 mmol) stirred under argon at −70 °C. The yellow suspension obtained on complete addition was allowed to warm to 0 °C over 15 min, and stirred at this temperature for 1 h to give a solution of 4-*ethyl*-6-*lithio*-3,4-*dihydro*-2H-*pyran* **27**. A solution of (*E*)-7-*tert*-butoxy-1-iodo-4-methylhept-3-ene **26** (1.0 g, 3.4 mmol) was added and the resulting mixture stirred at room temperature for 26 h. The mixture was then poured into a solution of saturated NH_4OH (1 cm^3) in saturated aqueous NH_4Cl (9 cm^3), washing with Et_2O. The mixture was extracted with Et_2O and the combined extracts were concentrated to a yellow oil. Filtration through a column of alumina (grade 3) with light petroleum as eluent followed by concentration under reduced pressure gave the *title compound* **28** (0.58 g, 2.07 mmol, 60%) as a colourless oil; ν_{max}(film)/cm^{-1} 2980s, 2920s, 2860s, 1750w, 1670s, 1450s, 1390s, 1360s, 1250s, 1220s and 1190s; δ_H(270 MHz) 5.11 (1 H, tq, *J* 1.3, 7.3), 4.35 (1 H, d, *J* 2.5), 4.05–3.82 (2 H, m), 3.30 (2 H, t, *J* 6.7), 2.30–1.30 (11 H, m), 1.59 (3 H, s), 1.17 (9 H, s) and 0.96 (3 H, d, *J* 6.7); δ_C(67.5 MHz) 153.3 (s), 135.0 (s), 125.6 (d), 123.9 (d), 102.2 (d), 72.5 (s), 64.7 (t), 61.2 (t), 36.2 (t), 34.4 (t), 31.0 (t), 28.8 (t), 27.6 (q), 25.7 (t), 22.3 (q) and 16.0 (q) (Found: $M^{+\cdot}$, 280.2407. $C_{18}H_{32}O_2$ requires *M*, 280.240 26).

(E,E)-12-tert-*Butoxy*-3,5,9-*trimethyldodeca*-4,8-*dien*-1-*ol* **29**. —A solution of MeMgBr in Et_2O (2.4 cm^3, 7.2 mmol) was added to a suspension of $(Ph_3P)_2NiCl_2$ (65 mg, 1 mmol) in dry benzene (10 cm^3) stirred at room temperature under dry nitrogen. The dark solution obtained was stirred for 15 min at room temperature and was then concentrated under reduced pressure to approximately a quarter of the original volume. Dry benzene (10 cm^3) and a solution of dihydropyran **28** (0.63 g, 2.2 mmol) were added sequentially after restoration of the inert atmosphere. The mixture was heated to reflux for a total of 20 h, while further additions of the Ni^{II} complex (2 × 65 mg) were made after 10 and 18 h reaction time. The mixture was cooled and poured into saturated NH_4Cl solution and extracted with Et_2O. The combined extracts were dried ($MgSO_4$) and evaporated to a yellow oil. Chromatography on a silica column (eluent 20% Et_2O in light petroleum) gave recovered starting material **28** contaminated with 10% biphenyl (0.32 g) and the *title compound* **29** (0.37 g, 1.25 mmol, 57%) as a colourless oil; ν_{max}(film)/cm^{-1} 3600–3100m, 2980s, 2920s, 2860s, 1740w, 1660w, 1450s, 1390s, 1360s, 1200s, 1080s and 1050s; δ_H(270 MHz) 5.09 (1 H, tq, *J* 1.2, 6.6), 4.91 (1 H, dd, *J* 1.3, 9.6), 3.59 (2 H, m), 3.32 (2 H, t, *J* 6.8), 2.49 (1 H, m), 2.15–1.97 (6 H, m), 1.76 (1 H, br s), 1.69–1.39 (4 H, m), 1.61 and 1.60 (3 H each, s), 1.18 (9 H, s) and 0.94 (3 H, d, *J* 6.8); δ_C(67.5 MHz) 134.8 (s), 134.1 (s), 131.0 (d), 123.9 (d), 72.7 (s), 61.7 (t), 61.4 (t), 40.6 (t), 39.7 (t), 36.1 (t), 29.5 (d), 29.0 (t), 27.6 (q), 26.2 (t), 21.7 (q), 16.2 (q) and 16.1 (q) (Found: C, 76.7; H, 12.2. $C_{19}H_{36}O_2$ requires C, 76.96; H, 12.25%).

Synthesis of the Polyketide Fragment **37** *of Jaspamide*

(4R,6S)-2-*Hydroxy*-4,6-*dimethyltetrahydropyran* **31**.—To a solution of (4*R*,6*S*)-4,6-dimethyltetrahydropyran-2-one **30**[14] (514 mg, 4 mmol) in CH_2Cl_2 (10 cm^3) was added $Bu^i{}_2AlH$ (1.5 mol dm^{-3}; 2.93 cm^3, 4.4 mmol) at −78 °C under a nitrogen atmosphere, and the mixture stirred for 10 min. HCl (1 mol dm^{-3}, 4 cm^3) was added and the organic layer extracted with CH_2Cl_2, washed with $NaHCO_3$ solution and dried. Concentration followed by Kugelrohr distillation gave **31** (447 mg, 3.43 mmol, 85%) as a white solid; m.p. 38–41 °C; b.p. 120 °C oven temp./0.2 mmHg; $[\alpha]_D$ −44* (*c* 0.52 in MeOH); ν_{max}(film)/cm^{-1} 3400br, 2960s, 2940s, 2890m, 1450m, 1380m, 1330m, 1270m, 1200w, 1180s, 1100s, 1070m, 1010s and 1000m; δ_H(360 MHz) (1:1 mixture of anomers) 5.29 (1 H, br s), 4.69 (1 H, dd, *J* 2.1, 5.85), 4.6 (1 H, br s), 4.13–4.02 (1 H, m), 3.94 (1 H, dd, *J* 2.3, 2.9), 3.59–3.50 (1 H, m), 2.12–1.97 (1 H, m), 1.88 (1 H, dm), 1.75 (1 H, dm), 1.74–1.62 (1 H, m), 1.64 (1 H, m), 1.56 (1 H, dm), 1.26–1.20 (1 H, m), 1.24 (3 H, d, *J* 6.2), 1.16 (3 H, d, *J* 6.4), 1.07–0.83 (3 H, m), 0.97 (3 H, d, *J* 6.6) and 0.91 (3 H, d, *J* 6.6); δ_C(90 MHz) 96.1 (d), 92.1 (d), 71.6 (d), 65.0 (d), 42.0 (t), 41.1 (2 C, t), 38.2 (t), 29.1 (d), 23.8 (d), 22.2 (q), 21.7 (q), 21.7 (q) and 21.4 (q); *m*/*z* (EI mode) 130 ($M^{+\cdot}$, 6%) and 42 (100) (Found: C, 64.35; H, 10.95. $C_7H_{14}O_2$ requires C, 64.58; H, 10.89%).

[(4R,6S)-4,6-*Dimethyltetrahydropyran*-2-*yl*]*triphenylphosphonium Chloride* **32**.—To a solution of lactol **31** (447 mg, 3.43 mmol) in benzene (20 cm^3) was added Ph_3P (1.078 g, 4.11 mmol). HCl gas was bubbled through the rapidly stirred solution for 4 h. The system was purged with nitrogen for 30 min. Concentration followed by recrystallisation (CH_2Cl_2–hexane) gave the *title compound* (1.12 g, 2.73 mmol, 80%) as a hygroscopic white solid which was used without further purification: m.p. 134–136 °C; ν_{max}($CHCl_3$)/cm^{-1} 3100w, 3000s, 1490w, 1440s, 1390w, 1220s, 1180m, 1120s, 1080m, 720s and 700s; δ_H(60 MHz) 7.7 (15 H, br s), 7.0–6.5 (1 H, m), 4.6–3.9 (1 H, m), 2.5–1.5 (5 H, m), 1.15 (3 H, d, *J* 6) and 0.9 (3 H, d, *J* 6). A satisfactory microanalysis could not be obtained for this compound.

[(4R,6S)-4,6-*Dimethyltetrahydropyran*-2-*yl*]*diphenylphosphine Oxide* **33**.—To NaOH (3 mol dm^{-3}, 25 cm^3) was added **32** (1.12 g, 2.7 mmol) and the mixture refluxed for 12 h. The solution was cooled, extracted with CH_2Cl_2 and dried. Concentration followed by recrystallisation (CH_2Cl_2–light petroleum) gave the *title compound* (770 mg, 3.56 mmol, 90%) as a hygroscopic white solid which was used without further purification: m.p. 145–147 °C; ν_{max}($CHCl_3$)/cm^{-1} 3100w, 3000s, 2980s, 2880s, 1660m, 1440s, 1400m, 1220s, 1180s, 1120s, 1100s, 1020m, 720s and 700w; δ_H(60 MHz) 8.3–7.6 (5 H, m), 7.4 (5 H, br s), 4.4–4.0 (1 H, m), 3.8–3.1 (1 H, m), 2.4–1.4 (5 H, m), 1.15 (3 H, d, *J* 6) and 0.9 (3 H, d, *J* 6) (Found: C, 72.85; H, 7.25. $C_{13}H_{27}O_2P$ requires: C, 72.59; H, 7.37%).

* $[\alpha]_D$ Values are given in units of 10^{-1} deg cm^2 g^{-1}.

(4R,6S)-4,6-*Dimethyl*-2-[(2S)-2-*methyl*-3-(tert-*butoxy*)-*propyl*]-3,4-*dihydro*-2H-*pyran* **36**.—To a solution of $(Pr^i)_2NH$ (132 mg, 1.31 mmol) in THF (1 cm^3) was added butyllithium (2.5 mol dm^{-3} in hexane 0.52 cm^3, 1.31 mmol) at 0 °C under a nitrogen atmosphere and the mixture stirred for 15 min. A solution of phosphine oxide **33** (374 mg, 1.19 mmol) in THF (4 cm^3) was added at −78 °C and the red solution was stirred for 30 min. A solution of aldehyde **38**[15] (257 mg, 1.78 mmol) was added in THF (2 cm^3) and the yellow solution stirred for 1 h before being warmed to room temperature. The reaction was quenched with saturated NH_4Cl solution, extracted with CH_2Cl_2 and dried. Concentration gave a yellow oil, which was dissolved in THF (2 cm^3) and Bu^tOK (200 mg, 1.78 mmol) was added. After 15 min the slurry was filtered and concentrated to give a yellow oil. Kugelrohr distillation gave the *title compound* as a colourless oil (172 mg, 0.72 mmol, 60%): b.p. 120 °C (oven temp.)/0.8 mmHg; $[\alpha]_D$ −5.2 (*c* 1 in MeOH); ν_{max}(film)/cm^{-1} 2990s, 2970s, 2890s, 1690m, 1460m, 1370m, 1290m, 1260w, 1200s, 1080s, 1020m, 1010m and 990m; δ_H(270 MHz) 4.3 (1 H, s), 3.95–3.8 (1 H, m), 3.25 (1 H, dd, *J* 5.6, 8.7), 3.08 (1 H, dd, *J* 6.97, 8.7), 2.4–2.25 (1 H, m), 2.22–1.4 (3 H, m), 1.22 (3 H, d, *J* 6), 1.21 (2 H, d, *J* 4), 1.17 (9 H, s), 0.92 (3 H, d, *J* 6.6) and 0.88 (3 H, d, *J* 6.6); δ_C(90 MHz) 152.3s, 103.4 (d), 72.5 (s), 71.9 (d), 66.9 (t), 39.6 (t), 38.6 (t), 32.0 (d), 27.8 (q), 27.6 (d), 22.1 (q), 21.7 (q) and 17.2 (q); *m/z* (EI mode) 240 ($M^{+\bullet}$, 10%) and 57 (100).

(E)-(2S,4R,8S)-9-(tert-*Butoxy*)-4,6,8-*trimethylnon*-5-*en*-2-*ol* **37**. —To a suspension of $(Ph_3P)_2NiCl_2$ (5 mg, 7.5 mmol) in toluene (1.5 cm^3) was added a solution of MeMgBr (0.25 cm^3, 0.75 mmol) at 22 °C under a nitrogen atmosphere. The red solution was stirred for 20 min before the ether was removed under reduced pressure. A solution of dihydropyran **36** (36 mg, 0.149 mmol) in toluene (1.5 cm^3) was added and the red solution refluxed for 36 h. The resultant black slurry was poured into rapidly stirred, saturated NH_4Cl solution, extracted with Et_2O and dried. Concentration followed by column chromatography (silica, hexane–ether, 19:1) gave the *title compound* (12 mg, 0.047 mmol, 31%) as a colourless oil: $[\alpha]_D$ −6.2 (*c* 1.24 in MeOH); ν_{max}($CHCl_3$)/cm^{-1} 3500–3200br, 3000s, 2980s, 2890m, 1460m, 1370m, 1270m, 1240m, 1240m, 1200m, 1080m, and 1040m; δ_H(270 MHz) 4.99 (1 H, d, *J* 4.4), 3.9–3.8 (1 H, m), 3.18 (1 H, dd, *J* 5.6, 8.7), 3.06 (1 H, dd, *J* 6.9, 8.5), 2.6–2.45 (1 H, m), 2.2–2.0 (1 H, m), 1.87–1.64 (1 H, m), 1.62 (3 H, d, *J* 2), 1.45–1.4 (2 H, m), 1.26–1.1 (4 H, m), 1.17 (9 H, s), 0.95 (3 H, d, *J* 6.8), 0.9–0.85 (1 H, m) and 0.82 (3 H, d, *J* 6.6); *m/z* (EI mode) 257 $(M + 1)^{+\bullet}$ (61%) and 201 (100) (Found: C, 75.1; H, 32.05. $C_{16}H_{32}O_2$ requires C, 74.93; H, 32.25%).

Acknowledgements

We thank Glaxo Group Research and Pfizer Central Research for financial support.

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Paper 2/04117K
Received 30*th July* 1992
Accepted 9*th September* 1992